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Animal Model of Human Disease

Mucopolysaccharidosis Type VII (Sly Syndrome)

Beta-glucuronidase-Deficient Mucopolysaccharidosis in the Dog

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Biologic Features

Mucopolysaccharidosis (MPS) type VII (Sly syndrome) was first described in a mixed-breed dog in 1984.¹ Since then, an additional 19 affected dogs have been studied in the animal colony established at the University of Pennsylvania, School of Veterinary Medicine. All of the affected dogs were descendants of a single carrier female and were, therefore, homozygous for a single mutation in the β -glucuronidase gene. Typical features of the syndrome that were evident in affected dogs by 4 weeks of age included a shortened broad face, low-set ears, and a laterally broad chest. Diffuse corneal clouding was evident by 8 weeks of age. By 9 weeks of age, affected animals were approximately 50% smaller than littermates and had a disproportionately large head. Polymorphonuclear leukocytes and lymphocytes in peripheral blood smears contained coarse cytoplasmic granules (Alder-Reilly bodies) that stained metachromatically with toluidine blue. Affected animals also had a positive Berry spot test² for excessive urinary glycosaminoglycans (GAGs), which were shown to be chondroitin 4- and 6-sulfates and dermatan sulfate by cellulose acetate electrophoresis.¹ Signs of appendicular skeletal disease were first evident between 2 and 5 months of age, when affected animals could no longer stand, but were able to move in sternal recumbency and eat and drink indepen-

dently. Synovial joint capsules were swollen and fluctuant, with most joints extremely lax, easily subluxated, and crepitant. Radiographic features of the disease included severe, progressive, epiphyseal dysplasia and bilateral hip subluxation to complete luxation. Cardiac abnormalities were variable. Several affected animals had no clinical signs of heart disease by 2 years of age, whereas others had clinical signs of mitral insufficiency or patent ductus arteriosus in the first week of life.

Significant pathologic changes were present in many systems. Hepatomegaly, without splenomegaly, was present. The trachea in all animals was misshapen with variable degrees of narrowing resulting from overlapping tracheal rings. Atrioventricular heart valve leaflets and chordae tendinae were thickened, with the mitral valve being the most affected. The closure of the ductus arteriosus was incomplete, resulting in either a patent ductus arteriosus or a ductus diverticulum. The arch of the aorta was thickened to some degree in all animals. In dogs over 4 months of age, the synovial membranes were hyperplastic, and the articular cartilage and underlying bone of most synovial joints was eroded. Histologically, cytoplasmic vacuoles were present in central nervous system neurons, hepatocytes, Kupffer cells, keratocytes, retinal pigment epithelium, atrioventricular heart valve fibroblasts, aortic smooth muscle cells, leukocytes, chondrocytes, and synovial cells. By electron microscopy, the cytoplasmic inclusions were membrane bound (Figures

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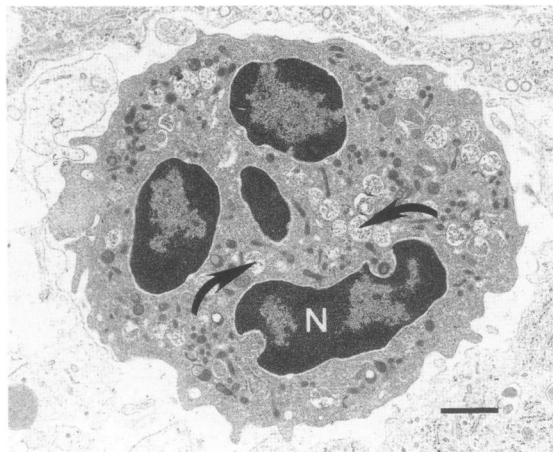


Figure 1. An electron photomicrograph of a polymorphonuclear leukocyte with membrane-bound cytoplasmic inclusions (arrows) from an 11-day-old dog with MPS VII (N, a lobe of the nucleus; bar = 1 μ) (lead citrate and uranyl acetate, $\times 7700$).

1 and 2) and were empty or contained granular or lamellar material.

Activity of β -glucuronidase in peripheral blood leukocytes and 10 other tissues ranged from 0.2% to 1.7% that of normal canine values.³ Canine MPS VII sera had about 6.4% of normal β -glucuronidase activity and was used to diagnose affected animals less than 3 weeks of age. Obligate heterozygotes for the disease had enzyme activities approximately 50% of normal.

Pedigree information (Figure 3) and enzyme activity of sera from family members were consistent with autosomal recessive inheritance. Male dogs of reproductive age were fertile by artificial insemination. Two female dogs were not observed to have estrus cycles by 24 months of age.

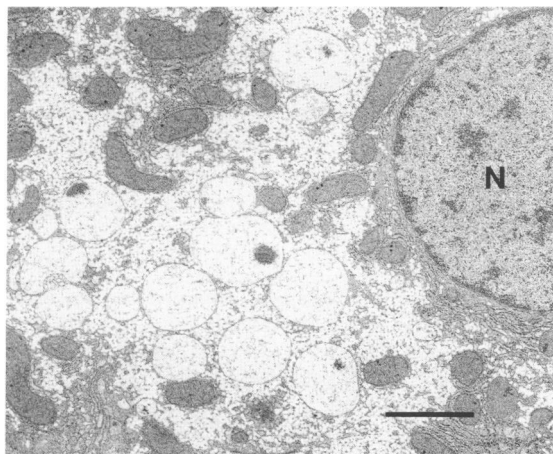


Figure 2. An electron photomicrograph of a hepatocyte from a 4-month-old dog with MPS VII. Note the large membrane-bound cytoplasmic inclusions containing fine granular material (N, nucleus; bar = 2 μ) (lead citrate and uranyl acetate, $\times 6000$).

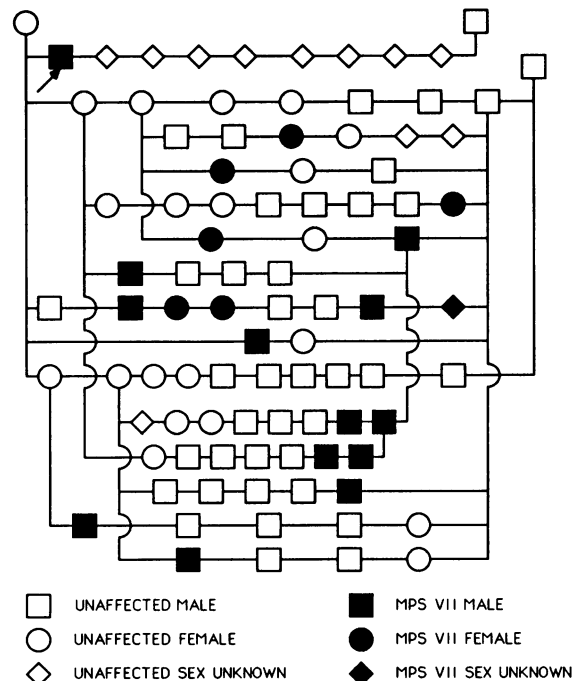


Figure 3. The pedigree of the family of dogs with MPS VII. The propositus (arrow) was reported to have been the offspring of a father-daughter mating, but that information could not be confirmed. All other affected dogs were descendants of a single heterozygous female and were therefore homozygous for the identical mutant allele. Affected males were able to reproduce by artificial insemination.

Comparison with Human Mucopolysaccharidosis VII

The clinical phenotype of MPS VII in man is variable.⁴ Patients range from those with severe mental retardation, skeletal abnormalities, corneal clouding, and hepatosplenomegaly to those with normal intelligence and stature, and little or no corneal clouding or skeletal abnormality. All human patients have had leukocyte inclusions and excreted excessive amounts of GAGs in their urine. The clinical phenotype in the dog most closely resembles the more severely affected human patients. Pathologic lesions of MPS VII in the dog and man are similar. In both species there is storage of incompletely degraded GAGs within membrane-bound cytoplasmic inclusions. The distribution of lesions in the dog also closely parallel those of the human mucopolysaccharidoses in general, and MPS VII in particular, affecting the skeletal, cardiac, ocular, and central nervous systems. This naturally occurring animal homolog is proving useful in studies of the pathogenesis and approaches to therapy for lysosomal storage diseases.^{5,6}

Availability of the Model

The colony of dogs is available for collaborative research. When the number of dogs with MPS VII exceeds the re-

search needs of the authors, animals will be made available to others with an interest in using this animal model.

Acknowledgments

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